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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

23565 7590 05/09/2006

KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,584	ALBERT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-41* is/are pending in the application.

4a) Of the above claim(s) *5-14,20 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,15-19,21 and 22* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 4 have been amended. Claims 1, 2 and 4-41 are pending. Claims 5-14, 20 and 23-41, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1, 2, 4, 15-19, 21 and 22 are under consideration.

Text of Title 35, U.S. Code not found in this action, can be found in a previous action.

In the prior Office action it was stated that the instant invention is not adequately supported by the priority documents 60/077,095, 60/101,749 or 60/075,356. This is re-affirmed. However, it is further noted that neither of 09/251,896 nor 09/565,958 identify the use of antagonists of FKBP or TOR nor the specific compounds of tacrolimus or rapamycin as useful for the inhibition of signaling consequent to dendritic cell-T cell engagement, and the resulting inhibition or elimination of effective CD+4 T cell help. Accordingly the instant invention will have a priority date commensurate with the instant filing date, March 12, 2001.

Claims 1, 2, 19, 21, 22 are rejected under 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368, cited in a previous Office action) in view of Albert et al, Nature, 1998, Vol. 392, pp. 86-89, cited in a previous action), Matzinger et al (U.S. 6,680,176) and Matzinger (Annual Review of Immunology, 1994, Vol.12, pp. 991-1045, cited in a previous action).

Claim 1 is drawn to a method for inducing tolerance in a mammal to an antigen comprising isolating dendritic cells from PBMC, exposing the dendritic cells ex vivo to apoptotic cells expressing said antigen in the presence of at least one dendritic cell maturation stimulatory molecule in the absence of effective CD+4 T cell help, wherein the absence of effective CD+4 T cell help is achieved by treating the dendritic cells with an agent that inhibits or eliminated effective CD+4 T cell help and introducing the resulting dendritic cells into said mammal wherein said dendritic cells induce apoptosis of antigen-specific CD+8 T cells in said mammal resulting in tolerance to said antigen. Claim 2 embodies the method of claim 1 wherein the dendritic cell maturation stimulatory molecule is PGE2, TNF-alpha, IL-6, IL-1 beta, LPS, monocyte-conditioned medium, CpG-DNA or any combination thereof. Claim 19 embodies the

method of claim 1 wherein the antigen is a tumor antigen, a viral antigen, a self antigen or a transplant antigen. Claim 21 embodies the method of claim 1 wherein after said dendritic cells mature and exhibit a CD14-, CD83+ phenotype, the dendritic cells are infused into a mammal. Claim 22 embodies the method of claim 1 wherein said mammal is a human.

Albert et al (JEM) teach that dendritic cells phagocytose apoptotic cells and Gross present antigens from the apoptotic cells to cytotoxic T-lymphocytes (abstract). Albert et al teach that dendritic cells can acquire antigens from tumors, transplants, infected cells and self tissues for stimulation or tolerization of CTLs (abstract), thus fulfilling the specific limitation of claim 19 specifying the types of antigen for which tolerance might be evoked. Albert et al teach the isolation of dendritic cells from peripheral blood and the use of monocyte conditioned medium (MCM) as a maturation factor for the dendritic cells thus fulfilling the specific embodiments of claim 2 (page 1360, first column, lines 12-14 under the heading of "Preparation of Cells"). Albert et al also teach that on days 10 and 11, the cells were of the mature phenotype CD14-, CD83+ and HLA-DR-hi (page 1360, first column, lines 15-17 under the heading "Preparation of Cells"). Albert et al also teach the maturation factors of LPS, ceramide, CD40L, TNF-alpha and PGE2 in addition to macrophage conditioned medium (page 1359, second column, lines 13-17). Albert et al teach that the co-culture of immature dendritic cells with apoptotic cells in the presence of macrophage conditioned medium , a maturation stimulus for dendritic cells, made apoptotic cells and even better target for Gross-presentation of antigen (page 1362, second column, lines 4-8). Albert et al do not teach the induction of tolerance by the exposure of dendritic cells to apoptotic cells in the absence of effective CD4 T cell help.

Albert et al (Nature) teach the Gross-priming of T-cells via apoptotic cells which are phagocytosed by dendritic cells (page 88, second column, lines 27-35). Albert et al teach that tolerance to an antigen may be dependent upon apoptotic cell death followed by antigen presentation by dendritic cells (page 88, second column, lines 35-38, 40-42). Albert et al conclude that the apoptosis dependent pathway has the potential to be manipulated to modulate immune response (page 88, second column, lines 43-46).

Matzinger et al teach that dendritic cells provide an activating signal which initially stimulated helper T cells, which in turn, stimulate and conditions said dendritic cell to a super activated state which can mediate direct activation of killer T cells and that this activation of

killer cells cam be carried out without need for the binary T-helper/APC/killer cell complexes (column 2, lines 63-67 and column 4, lines 14-19). Matzinger et al specifically teach that stimulation with a CD40 ligand turns a dendritic cell into a super activated APC that is able to prime naive killer cells (column 8, lines 17-19). Matzinger et al teach that compounds which are able to block the CD40 activation of dendritic cells by helper T cells can block, inhibit or prevent the activation of killer T cells (column 10, lines 48-51).

It would have been prima facie obvious at the time the claimed invention was made to use a compound which was able to block the CD40 activation of dendritic cells in the method of inducing tolerance to an antigen by exposing immature dendritic cells to said antigen ex vivo to facilitate the uptake and presentation of the apoptotic antigen by the dendritic cell, as taught by Albert (JEM and Nature). It would have been further obvious to provide a compound which would block the activation of CD40 by helper T cells as per the teachings of Matzinger et al in order to eliminate or inhibit the ability of the dendritic cell to stimulate CD+8 killer T cells. It would have been obvious to administer such treated dendritic cells into the patient in need thereof, because said dendritic cells will present antigen to CD+8 T cells but will not be able to activate said T cells, and therefore said T cells will undergo apoptosis in the absence of the stimulatory signal which must be provided in addition to the presentation of the appropriate antigen in the context of MHC (Matzinger, Annual Review of Immunology, 1994, Vol.12, pp. 991-1045, especially page 1001, lines 8-11) .

Claims 1, 2, 4, 15-17, 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368), Albert et al, Nature, 1998, Vol. 392, pp. 86-89) and Matzinger et al (U.S. 6,680,176) as applied to claims 1, 2 19, 21 and 22 above, and further in view of Klaus et al (European Journal of Immunology. 1994, Vol. 24, pp. 3229-3232) and the abstract of Panhans-Gross et al (Journal of Investigative Dermatology, April 1998, Vol. 110, page 630).

Claim 4 embodies the method of claim 1hwerein said agent is removed from the dendritic cells prior to exposure of said dendritic cells to the T cells. Claim 15 embodies the method of claim 4 wherein said agent inhibits signaling consequent to dendritic cell CD+4 T cell engagement. Claim 16 embodies the method of claim 15 wherein said agent is a FKBP

antagonist or a TOR antagonist. Claim 17 embodies the method of claim 16 wherein said FKBP antagonist is tacrolimus.

The specific embodiments of claims 1, 2, 19, 21 and 22 are rendered obvious by the combination of Albert (JEM), Albert (Nature) and Matzinger et al. None of the aforesaid references teaches tacrolimus as the agent required by the claimed method.

Klaus et al teach that FK506 (tacrolimus) blocks the resulting signal in a B cell which issues from the engagement of CD40 ligand on a T cell engaging CD40 on a B cell. Klaus does not specifically teach that FK506 can inhibit the signal resulting from the engagement of CD40 on a dendritic cell by CD40 ligand on a helper T-cell

The abstract of Panhans-Gross et al teaches that Langerhans cells treated with FK506 (tacrolimus) in vitro exhibit a dramatic decrease in allostimulatory capacity.

It would have been prima facie obvious to use FK506 as an agent which blocks CD40 activation to treat the dendritic cells made obvious by the combination of Albert (JEM) and Albert (Nature). One of skill in the art would have been motivated to do so by the specific teaching of Matzinger et al on the use of agents which block CD40 activation on dendritic cells to prevent or inhibit the activation of killer T cells. One of skill in the art would have had reasonable expectation of success in the blocking of the CD40 activation signal in dendritic cells by FK506 because Klaus et al teach that FK506 blocks the CD40 activation in B cells, and the abstract of Panhans-Gross et al teaches that FK506 can inhibit the activating power of Langerhans cells. One of skill in the art would know that Langerhans cells are a type of re-circulating dendritic cell. Thus, it would be reasonable to conclude, based on the combined teachings of Klaus et al and the abstract of Panhans-Gross et al that the FK506 would inhibit the CD40 activation signal in dendritic cells as well as in B cells.

Claims 1, 2, 4, 15-19, 21 and 22 rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368), Albert et al, Nature, 1998, Vol. 392, pp. 86-89) and Matzinger et al (U.S. 6,680,176) as applied to claims 1, 2 19, 21 and 22 above, and further in view of Klaus et al (European Journal of Immunology. 1994, Vol. 24, pp. 3229-3232) and the abstract of Panhans-Gross et al (Journal of Investigative

Dermatology, April 1998, Vol. 110, page 630). as applied to claims 1, 2, 4, 15-17, 19, 21 and 22 above, and further in view of Schreiber (Science, 1991, Vol. 251, pp. 283-287).

Claim 18 embodies the method of claim 16 wherein said TOR antagonist is rapamycin. Schreiber teaches that both FK506 and rapamycin inhibit T cell activation at comparable concentration (page 283, second column, lines 9-12). Schreiber teaches that both drugs contain a common element that binds to FKBP (page 286, first column, lines 44-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute rapamycin for FK-506 in the method rendered obvious by the combination of Albert (JEM), Albert et al (Nature), Matzinger, Klaus et al and the abstract of Panhans-Gross. One of skill in the art would have been motivated to do so by the teaching of Schreiber on the structural similarity of rapamycin to FK-506 and the ability of both drugs to inhibit T-cell activation.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
2/6/2006

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER